

**(12) INTERNATIONAL APPLICATION PUBLISHED ACCORDING TO THE
AGREEMENT
ON INTERNATIONAL COOPERATION IN THE FIELD OF PATENTS (PCT)**

**(19) World Organization for
Intellectual Property
International Office**



**(43) International Date of Publication
Number**

February 7, 2002 (2/7/2002)

PCT

(10) International Publication

WO 02/09731 A1

(51) International Patent Classification⁷:
A61K 33/00, 45/06, A61P 11/00

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(21) International File Number:
PCT/FR01/02396

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(22) International Date of Application:
July 23, 2001 (7/23/2001)

**(81) Intended states (national): AU, CA,
JP, US, ZA.**

(25) Language in which submitted: French

(26) Language in which published: French

**(84) Intended states (regional): European
Patent (AT, BE, CH, CY, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
TR).**

(30) Priority data: 00/09881
July 27, 2000 (7/27/2000) FR

Published:

- with International Search Report
- will be republished upon expiration of the
time provided for amendment of claims, if
these amendments are received

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*Please refer to the explanations "Guidance
Notes on Codes and Abbreviations" at the
beginning of each regular issue of the PCT
Gazette for an explanation of the two-letter
codes and of the other abbreviations.*

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**(54) Title: USE OF CO FOR TREATING INFLAMMATION OF UPPER AIRWAYS OR
BRONCHI**

(57) Abstract: [English abstract in the text]

Use of CO for treating inflammation of upper airways or bronchi.

This invention relates to the use of carbon monoxide (CO) of a CO donor to manufacture all or part of a medication intended for treating or preventing acute or chronic inflammatory pathologies or afflictions, especially all or part of a gaseous medication for inhalation.

Acute or chronic inflammatory pathologies or afflictions are presently treated with the help of various anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAID), steroidal anti-inflammatory drugs (SAID), or of other molecules known to have such action, for example nitrogen monoxide (NO).

However, these products cannot be considered to be totally satisfactory in the therapeutic sector since they either cause side effects for the patient or they have insufficient anti-inflammatory activity to be truly effective.

Thus, it is known that the nonsteroidal anti-inflammatory drugs have efficacy that is often in proportion to their gastrointestinal toxicity. In other words, their oral administration may entail gastric problems for the patient that are more or less severe, up to local hemorrhages of the gastrointestinal tract.

Otherwise, the steroidal anti-inflammatory drugs also cause numerous side effects, and especially a risk of addiction and accordingly a withdrawal obligation for the patient.

Besides, it has already been suggested to use nitrogen monoxide (NO) gas, by itself or in combination with an NO donor molecule, as an anti-inflammatory product, considering its probable role in the cascade of inflammation. In particular, it has already been suggested to use NO gas as a pulmonary vasodilator or bronchial dilator, as described in the document EP-A-560928.

Nitrogen monoxide (NO) has also been proposed, moreover, as a protector of the gastric mucosa during an oral administration in combination with a nonsteroidal anti-inflammatory product or products.

The document WO-A-97/37644, for its part, describes the use of NO or of carbon monoxide (CO) in the treatment of hemoglobinopathies.

More recently, endogenous carbon monoxide (CO) synthesized by body cells has been proposed as the principal path of the activity of heme oxidase, the basic molecule of the inflammatory system in mammals, with endogenous CO probably having activity as a modulator of heme oxidase.

Nevertheless, at this time there exists no therapeutic solution for the treatment of inflammation that is truly satisfactory when the efficacy of the treatment is related to the risk encountered by the patient, and in particular, there exists no therapeutic agent that has truly given proof of its efficacy by inhalation.

In other words, the problem that is faced is to propose a truly effective therapeutic composition for combating acute or chronic inflammatory pathologies, especially one that can be readily administered by inhalation.

The purpose of this invention is thus to solve the above problem, i.e. to propose a therapeutic product that provides for the effective treatment of inflammatory pathologies, which therapeutic product is also easy to produce on an industrial scale.

Furthermore, the product or the composition of the invention should be able especially:

- to act more upstream in the inflammation cascade and accordingly more effectively and at a smaller dose than the existing products,
- to be administered easily, preferably by inhalation, but possibly by other routes such as enteral and parenteral,

- and to be administered with no side effect for the patient, i.e. avoiding the hemorrhagic gastrointestinal problems such as those caused by the conventional nonsteroidal anti-inflammatory drugs.

The invention thus relates to the use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent combined with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation, bronchoconstriction, and/or vasoconstriction in humans or animals.

According to a second aspect, the invention also relates to the use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent combined with at least one active product with anti-inflammatory action to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation in humans or animals.

According to a third aspect, the invention relates to the use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent combined with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, and at least one active product with anti-inflammatory action to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation in humans or animals.

According to a fourth aspect, the invention also relates to the use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent combined with at least one active product chosen from among β_2 -stimulants, theophylline and derivatives, anticholinergic bronchodilators, and cromones to manufacture a medication or part of a medication intended for treating or preventing bronchoconstriction and/or vasoconstriction in humans or animals.

According to a fifth aspect, the invention also relates to the use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent combined with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, and at least one active product chosen from among the β_2 -stimulants, theophylline and

derivatives, anticholinergic bronchodilators, and cromones, to manufacture a medication or part of a medication intended for treating or preventing bronchoconstriction and/or vasoconstriction in humans or animals.

In the context of the invention, "carbon monoxide (CO) donor agent" means one or more molecules or one or more products or substances capable of fixing and/or transporting one or more molecules of CO and subsequently liberating and/or releasing said molecule or molecules of CO, in particular after its administration to humans or to animals, for example at or in the target organ to be treated.

In the same way, the term "manufacture" is considered in its most generic sense and is considered to be totally equivalent to similar terms such as "prepare."

In other respects, it goes without saying that endogenous CO, i.e. the CO synthesized directly by the human or animal body, is excluded from this invention.

Depending on the case, the use of the invention may include one or more of the following characteristics:

- the carbon monoxide (CO) or the carbon monoxide (CO) donor is in the gaseous form.
- the medication or the part of said medication also contains at least one additional gas chosen from among xenon, hydrogen, nitrous oxide (N₂O), argon, neon, krypton, carbonaceous hydrocarbons or fluorocarbons, and mixtures of a plurality of these gases. The usable carbonaceous hydrocarbons or fluorocarbons are conventionally gases or gaseous mixtures based on heptafluoropropane, tetrafluoroethane, or other similar gases that may also contain hydrogen.
- the active product with anti-inflammatory action is chosen from among the steroidal anti-inflammatory drugs (SAID), in particular corticosteroids and mineralosteroids such as prednisone, dexamethasone and methylprednisolone.

- the active product with anti-inflammatory action is chosen from among the nonsteroidal anti-inflammatory drugs (NSAID).

- the active product is chosen from among the indoles and derivatives, for example indomethacin; the arylcarboxylics, for example ketoprofen or arylpropionic acid; the oxicam derivatives such as piroxicam or the fenamates; the salicylates, for example acetylsalicylic acid, theophylline and derivatives, anticholinergic bronchodilators, and the cromones, such as cromoglycate, and mixtures thereof.

- the active product is chosen from among the anticholinergic bronchodilators such as ipratropium bromide, theophylline and derivatives, anticholinergic bronchodilators, and cromones such as cromoglycate,

- the medication or the part of the medication is in inhalable form, preferably in gaseous form or in aerosol form.

- the β_2 -stimulants, for example, are chosen from among the following compounds: terbutalin, salbutamol, and salmeterol.

- the medication is intended for treating or preventing inflammatory pathology, vasoconstriction, or bronchoconstriction of the upper airways or of the bronchial tree in humans or animals, preferably a pathology from among asthma, pneumopathies, mucoviscidosis, and bronchopneumopathies.

- the medication is intended for treating or preventing systemic inflammatory pathology of the type of arthritic polyarteritis (AP), rheumatoid polyarthritis (RP), and articular rheumatism.

- the carbon monoxide (CO) or the carbon monoxide donor agent enters into the composition of a medication that can be administered by inhalation, enterally, parenterally, transcutaneously, or transdermally.

- the medication contains a therapeutically effective quantity of carbon monoxide (CO), and preferably the quantity of CO is between 1 ppb and 1000 ppm, preferentially below 600 ppm.

In other respects, the invention relates to a gaseous mixture chosen from among CO/O₂, CO/N₂, CO/NO/N₂, CO/CO₂, CO/He, CO/N₂O, Ar/CO, Kr/CO, Ne/CO mixtures, as a medication or as part of a medication to be inhaled; said mixture may also contain from 10 to 30% by volume of oxygen, for example a CO/N₂O/O₂ or CO/He/O₂ mixture.

For example the gaseous mixture contains (by volume) from 100 ppb to 600 ppm of NO, less than 10% of CO₂, from 20 to 85% of helium, from 18 to 50% of oxygen, and from 10 to 99.999% of nitrogen.

According to still another aspect, the invention also relates to the medicinal or pharmaceutical preparation in the form of a gaseous mixture or of an aerosol containing a therapeutically effective proportion of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent and:

at least one vector and/or propellant gas chosen from among helium, oxygen, nitrogen, xenon, hydrogen, carbon dioxide, argon, nitrogen monoxide (NO), nitrous oxide (N₂O), carbonaceous hydrocarbons, fluorocarbons, and mixtures of a plurality of these gases

and/or at least one active product chosen from among the β_2 -stimulants, theophylline and derivatives, anticholinergic bronchodilators, and cromones,

and/or at least one active product with anti-inflammatory action chosen from among nonsteroidal anti-inflammatory drugs (NSAID) and steroidal anti-inflammatory drugs (SAID).

In summary, this invention is based on the discovery by the inventors that carbon monoxide (CO), commonly put forward as a toxic gas, can be used for therapeutic purposes, and more precisely that CO can have therapeutic activity through its antiproliferative, platelet anti-aggregating, anti-inflammatory, bronchodilative, and vasodilative properties.

Therefore, carbon monoxide (CO) can be used to combat varied problems or pathologies that cause inflammatory reactions in humans, for example certain respiratory insufficiencies, especially acute asthma, obstructive bronchopneumopathy (OBP), and any other clinical manifestation linked to bronchial obstruction.

Actually, it is known that in the case of asthma and several other similar obstructive pathologies, bronchoconstriction and the inflammatory changes of the bronchial mucosa, on the one hand, and the hypersecretion of mucus on the other hand, cause an increase of the resistance of the airways to the flow of respiratory gases, principally air, i.e. a proliferation of the cells that particularly form the bronchi and bronchioles.

This then entails additional respiratory work on the part of the patient since he/she is forced to increase his/her respiratory work to succeed in holding constant his/her inspiratory and expiratory flow rate.

This excessive work then quickly involves a strain and exaggerated fatigue of the respiratory muscles.

Furthermore, inflammatory reactions also take place in the bronchi and bronchioles.

Consequently, administration of CO to the patient should provide for effectively combating these phenomena thanks to the antiproliferative, platelet anti-aggregating, anti-inflammatory, bronchodilative, and vasodilative activity of CO.

Actually, the molecule of CO acts essentially in two ways on the inflammatory process, as follows:

- CO selectively inhibits the expression of pro-inflammatory agents such as TNF-alpha, interleukin-1 beta, and macrophage inflammatory-1 beta. These agents customarily play an important role in the inflammatory process.

- CO activates and modulates the liberation of anti-inflammatory agents such as interleukin 10.

Nevertheless, although the mode of action of CO is not totally known as yet, it is probable that it is not necessarily linked to the CGMP-cycle path as demonstrated with NO.

The activity of CO is more probably linked to another path involving an activated mitogenic protein kinase (AMP).

This anti-inflammatory activity by a path other than the CGMP cycle helps the combination of the two gaseous molecules NO and CO. It is logical to think that the anti-inflammatory action of the NO/CO mixture is greater than that of the two molecules taken separately; in other words, that these two molecules act synergistically.

Accordingly, it can be said that the use of CO, optionally coupled with NO, opens up new therapeutic possibilities in the field of inflammation.

The CO can be administered by the inhalation route, i.e. CO is administered to the patient via his respiratory tract by means of a CO supply device, such as a respiratory assistance ventilator to which is connected a source of CO so as to administer the CO to the patient through a respiratory mask, respiratory goggles, or a cannula.

Gaseous CO can be administered either continuously or in pulses, i.e. during all or part of each inspiratory phase of the patient. In the second case, the beginning and/or the end of each inspiratory and/or expiratory phase is traditionally detected by means of a device suitable for the purpose.

When CO is delivered in the gaseous form to a patient, care is taken that the respiratory gas administered to the patient, besides the CO or the CO donor, also contains oxygen in non-hypoxic amounts, i.e. in a proportion sufficient to assure proper ventilation of the patient, like that of air or a gaseous mixture containing on the order of 19 to 23% oxygen, the rest being one or more inert gases such as nitrogen.

In other respects, as explained above, carbon monoxide (CO) or the carbon monoxide (CO) donor agent is used pursuant to the invention in combination with one or more other gases and/or with at least one active product with anti-inflammatory action.

Actually, such use in combination can lead to a substantial amelioration of the effect of the active product with anti-inflammatory action in the presence of CO compared to use of the same product but without CO.

In other words, through its aforementioned properties, CO sometimes leads to an ameliorating or synergistic effect on the action of the active product by easing the assimilation of said active product by the patient.

The same applies to the combination of CO with certain gases such as NO.

It should be stated that the medicinal mixtures pursuant to the invention can be manufactured not only directly at their point of use and just before their administration to the patient, but also in a production site for pharmaceutical products, such as a pharmaceutical production laboratory, before being conveyed in finished form to their point of use.

Claims

1. Use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent in combination with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation, bronchoconstriction, and/or vasoconstriction.
2. Use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent in combination with at least one active product with anti-inflammatory action to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation.
3. Use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent in combination with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, and at least one active product with anti-inflammatory action to manufacture a medication or part of a medication intended for treating or preventing acute or chronic inflammation.
4. Use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent in combination with at least one active product chosen from among β_2 -stimulants, theophylline and derivatives, anticholinergic bronchodilators, and cromones to manufacture a medication or part of a medication intended for treating or preventing bronchoconstriction and/or vasoconstriction.
5. Use of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent in combination with at least one gas chosen from among nitrogen monoxide (NO), carbon dioxide (CO₂), helium, oxygen, nitrogen, and mixtures thereof, and at least one active product chosen from among β_2 -stimulants, theophylline and derivatives, anticholinergic bronchodilators, and cromones, to manufacture a medication or part of a medication intended for treating or preventing bronchoconstriction and/or vasoconstriction.

6. Use pursuant to one of the claims 1 to 5, in which the carbon monoxide (CO) or the carbon monoxide (CO) donor agent is in the gaseous form.

7. Use pursuant to one of the claims 1 to 6, in which the medication or the part of said medication also contains at least one additional gas chosen from among xenon, hydrogen, argon, krypton, neon, nitrous oxide (N₂O), carbonaceous hydrocarbons, or fluorocarbons, and mixtures of a plurality of these gases.

8. Use pursuant to one of the claims 1 to 3, in which the active product with anti-inflammatory action is chosen from among steroidal anti-inflammatory drugs (SAID), in particular corticosteroids and mineralosteroids.

9. Use pursuant to one of the claims 1 to 3, in which the active product with anti-inflammatory action is chosen from among nonsteroidal anti-inflammatory drugs (NSAID).

10. Use pursuant to one of the claims 1 to 3 and 9, in which the active product is chosen from among the indoles and derivatives, arylcarboxylics, oxicam derivatives, salicylates, β_2 -stimulants, theophylline and derivative, anticholinergic bronchodilators, cromones, and mixtures thereof.

11. Use pursuant to one of the claims 1, 4, and 5, in which the active product is chosen from among the anticholinergic bronchodilators.

12. Use pursuant to one of the claims 1 to 11, in which the medication or part of the medication is in inhalable form, preferably in gaseous form or aerosol form.

13. Use pursuant to one of the claims 1 to 12, in which the medication is intended for treating or preventing an inflammatory pathology, vasoconstriction, or bronchoconstriction of the upper airways or of the bronchial tree in humans or animals, preferably a pathology chosen from among asthma, mucoviscidosis, pneumopathies, and bronchopneumopathies.

14. Use pursuant to one of the claims 1 to 12, in which the medication is intended for treating or preventing a systemic inflammatory pathology, in particular of the type of arthritic polyarteritis (AP), rheumatoid polyarthritis (RP), and articular rheumatism.

15. Use pursuant to one of the claims 1 to 14, in which the carbon monoxide (CO) or the carbon monoxide (CO) donor agent enters into the composition of a medication that can be administered by inhalation, enterally, parenterally, transcutaneously, or transdermally.

16. Use pursuant to one of the claims 1 to 15, in which the medication contains a therapeutically effective quantity of carbon monoxide (CO), preferably a quantity of CO between 1 ppb and 1000 ppm, preferentially less than 600 ppm.

17. Gaseous mixture chosen from among CO/O₂, CO/N₂, CO/NO/N₂, CO/CO₂, CO/He, CO/N₂O, Ar/CO, Kr/CO, Ne/CO mixtures as the medication or part of the medication to be inhaled, with said mixture preferably also containing from 10 to 30% by volume of oxygen.

18. Medicinal or pharmaceutical preparation in the form of a gaseous mixture or of an aerosol containing a therapeutically effective proportion of carbon monoxide (CO) or of a carbon monoxide (CO) donor agent and

- at least one vector and/or propellant gas chosen from among helium, oxygen, nitrogen, xenon, hydrogen, carbon dioxide, argon, nitrogen monoxide (NO), nitrous oxide (N₂O), carbonaceous hydrocarbons, fluorocarbons, and mixtures of a plurality of these gases,

- and/or at least one active product chosen from among β_2 -stimulants, theophylline and derivatives, anticholinergic bronchodilators, and cromones,

- and/or at least one active product with anti-inflammatory action chosen from among the nonsteroidal anti-inflammatory drugs (NSAID) and the steroidal anti-inflammatory drugs (SAID).

[International Search Report attached in English (2 pages) and French (2 pages)]